REMARKS

Applicants respectfully thank the Examiner for reconsidering and removing the previous obviousness rejection. The Patent Office now has rejected all the pending claims (claims 1-20) under 35 USC § 103 (a) as being unpatentable over Straub et al. (US Pat. App. Pub. No. 20030153610) in view of Yamamoto et al. (US Patent 6,514,529) and Martin et al. (US Patent 4,344,934). Reconsideration and removal of the rejection is respectfully requested for the following reasons.

The Claimed Invention

Claims 1-20 concern a novel pharmaceutical formulation of an active compound (I) that is 5-chloro-*N*-({5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidin-5-yl}-methyl)-2-thiophenecarboxamide, also known as rivaroxaban. Applicants found surprisingly that preparing granules comprising rivaroxaban in hydrophilized form by moist granulation leads to a significant increase in bioavailability. Page 2, lines 5-9.

The Rejection

The Patent Office finds that Straub et al. disclose the oxazolidinone compound of the present claims and its use as a pharmaceutical product for thromboembolic diseases. The Office relies on Yamamoto as allegedly disclosing a solid, oral pharmaceutical composition of another oxazolidinone– the antibiotic linezolid –in hydrophilized and crystalline form with hydroxypropylmethylcellulose as a binding agent. Martin is relied upon for allegedly also teaching a pharmaceutical dosage form in which the active agent is hydrophilized, and in which sodium lauryl sulphate and hydroxypropylmethylcellulose are present. The Patent Office asserts that it would have been obvious to modify Straub et al. to use the formulation of Yamamoto with rivaroxaban because the compounds are structurally very similar and linezolid is poorly water soluble, and to modify Straub et al. with the formulation in Martin because Martin allegedly discloses that its process can be used with poorly water-soluble antibiotics and other active agents.

For the following reasons, Applicants disagree.

Straub et al. and Yamamoto

Applicants respectfully disagree with the Office's characterization of Yamamoto and with the alleged rational to modify Straub et al. to use the Yamamoto formulation.

First, rivaroxaban as in the present claims has much lower water solubility than linezolid as discussed in Yamamoto. The Patent Office states that linezolid is poorly water soluble, which it is not. On the contrary, linezolid has a solubility of 3 mg/ml (corresponding to 3000 mg/l). As shown in the product literature for a commercial linezolid product ZYVOXID, it is sold as an infusion solution in water containing 2 mg/ml. See ZYVOXID product literature, submitted with IDS of July 26, 2010. Rivaroxaban, in contrast, is poorly water soluble having only 7 mg/l solubility. Its solubility is more than 400 fold worse than linezolid.

According to the standards employed in the British Pharmacopoeia 2009, linezolid is "slightly soluble" and rivaroxaban, in contrast, is "practically insoluble." See British Pharmacopoeia 2009 Online (www.bpclab.co.uk), Part II, General Notices Part II, Official Standards, Characteristics of Solubility, relevant pages submitted herewith.

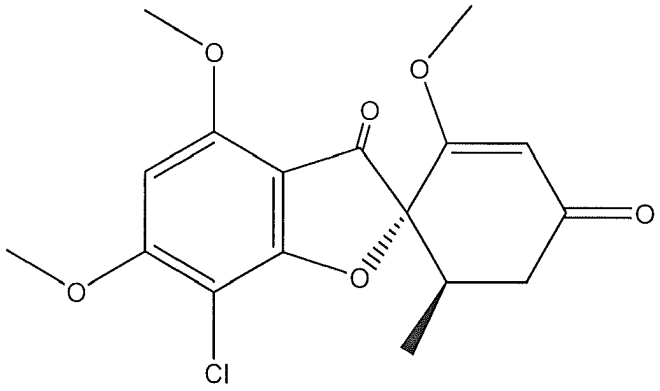
A person of ordinary skill in the art of pharmaceutical formulation would see this great discrepancy between solubility and would not be motivated to substitute the poorly soluble rivaroxaban in the formulation of the water soluble linezolid.

Furthermore, the Patent Office finds motivation to combine Straub et al. and Yamamoto in the "striking similarity" of the structures. Yet the dramatically different solubilities of the two compounds show that even structures sharing a common core nevertheless can have very different physical properties. The solubility differences rebut any suggestions that structural similarities would have motivated a skilled artisan to modify Straub et al. to use the Yamamoto formulation.

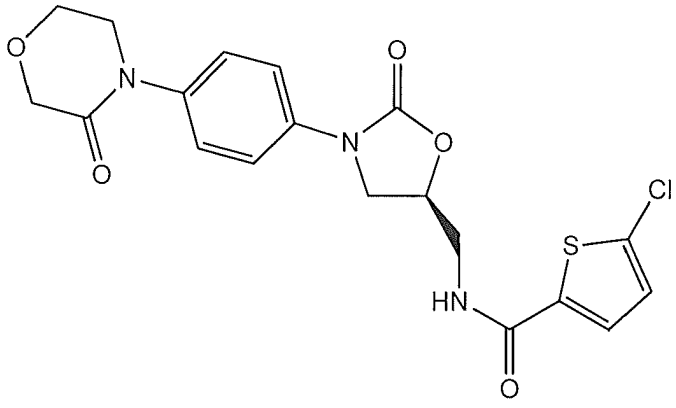
Straub et al. and Martin

The Patent Office alleges that one of ordinary skill would have been motivated to substitute rivaroxaban as disclosed in Straub et al. for the hydrophilized, crystalline and micronized griseofulvin taught in Martin because Martin teaches that its process can be used

with poorly water-soluble antibiotics and other active agents. Yet Martin is primarily concerned with formulation of griseofulvin. Griseofulvin has the following structure, which is very different from rivaroxaban as found in the present claims:



Rivaroxaban has the following structure:



Thus, there would not be even a prima facie reason based on structure to use the Martin formulation with rivaroxaban.

Martin teaches that its compositions of poorly soluble or water insoluble drugs "provide higher dissolution rates in vivo" as well as higher bioavailability. Col. 3, lines 14-16. The examples report as conclusions that the ultramicrocrystalline griseofulvin produced in the example "has a much faster dissolution rate into water at 37°C than microsized griseofulvin...." See, e.g., Col. 7, lines 33-37 (example 2) and examples 3-5 and 7-15. Many examples further

state that the ultramicrocrystalline griseofulvin also has a superior dissolution rate to the microsized or untreated griseofulvin. Examples 2, 7-13. Thus, Martin suggests that its process improves dissolution rate. Although most of Martin's examples are with unformulated powdered griseofulvin, in example 17 Martin reports that the dissolution profile for direct compression tablets demonstrated no significant differences in dissolution for the formulated tablet as compared with the unformulated powdered material.

In contrast to Martin's teaching of how to improve the dissolution profile, rivaroxaban tablets prepared by direct tabletting already had a good dissolution profile. Specification, pp. 10-11. Because the tablet dissolution rate was already good, the skilled artisan would not have been motivated to follow the process in Martin, which is taught to improve dissolution rate. The reasonable artisan would not have had any expectation of success in using the Martin teachings, because dissolution rate was already good. Martin exemplifies improvement in bioavailability with improvement in dissolution. Where dissolution rate is not a problem, then there is no suggestion to the ordinary skilled person that bioavailability can be increased by the method in Martin.

Applicants compared directly tabletted rivaroxaban with tabletted hydrophilized rivaroxaban and found surprisingly that in spite of slower disintegration of the hydrophilized rivaroxaban composition, and in spite of very similar in vitro release rates, the hydrophilized composition has marked advantages in absorption and thus a bioavailability increase of about 35%. Page 11, lines 3-5.

CONCLUSION

For these reasons, allowance of the claims is respectfully requested. Alternatively, if any issues remain, the Examiner is urged to call the undersigned attorney to resolve them. No fees are believed due with the filing of this paper. However, if a fee is due, please charge our Deposit Account No. 03-2775, under Order No. 11987- 00043-US from which the undersigned is authorized to draw.

Dated: November 1, 2010

Respectfully submitted,

By 

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